



This is a repository copy of *A novel mutation in the FGD4 gene causing Charcot-Marie-Tooth disease.*

White Rose Research Online URL for this paper:  
<http://eprints.whiterose.ac.uk/117077/>

Version: Accepted Version

---

**Article:**

Zis, P., Reilly, M.M., Rao, D.G. et al. (3 more authors) (2017) A novel mutation in the FGD4 gene causing Charcot-Marie-Tooth disease. *Journal of the Peripheral Nervous System*. ISSN 1085-9489

<https://doi.org/10.1111/jns.12222>

---

**Reuse**

Items deposited in White Rose Research Online are protected by copyright, with all rights reserved unless indicated otherwise. They may be downloaded and/or printed for private study, or other acts as permitted by national copyright laws. The publisher or other rights holders may allow further reproduction and re-use of the full text version. This is indicated by the licence information on the White Rose Research Online record for the item.

**Takedown**

If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing [eprints@whiterose.ac.uk](mailto:eprints@whiterose.ac.uk) including the URL of the record and the reason for the withdrawal request.



[eprints@whiterose.ac.uk](mailto:eprints@whiterose.ac.uk)  
<https://eprints.whiterose.ac.uk/>

**Authors**

Panagiotis Zis<sup>1,2</sup>, – Corresponding Author

Mary M Reilly<sup>3</sup>,

Dasappaiah G Rao<sup>1</sup>,

Pedro Tomaselli<sup>3</sup>,

Alex M Rossor<sup>3</sup>,

Marios Hadjivassiliou,<sup>1,2</sup>

**Affiliations**

1. Academic Department of Neurosciences, Sheffield Teaching Hospitals NHS Foundation Trust
2. University of Sheffield
3. MRC Centre for Neuromuscular Diseases, UCL Institute of Neurology, Queen Square, London WC1N 3BG, UK.

**Corresponding author's contact details**

Academic Department of Neurosciences

Royal Hallamshire Hospital

Glossop Rd, Sheffield, South Yorkshire S10 2JF

Email: [takiszi@gmail.com](mailto:takiszi@gmail.com)

**Running title:** CMT and FGD4 gene mutations

**Key words:** CMT; neuropathy; mutation; FGD4 gene

**Ethical publication statement:**

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

**Author Contributions**

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/jns.12222

Panagiotis Zis: drafting/revising the manuscript, clinical management of the case, accepts responsibility for conduct of research and final approval.

Mary Reilly: genetic analysis, revising the manuscript

Dasappaiah Ganesh Rao: clinical management of the case, revising the manuscript

Pedro Tomaselli: genetic analysis, revising the manuscript

Alex Rossor: genetic analysis, revising the manuscript

Marios Hadjivassiliou: drafting/revising the manuscript, clinical management of the case, accepts responsibility for conduct of research and final approval.

### **Disclosures**

MMR, AR and PT are grateful to the Medical Research Council (MRC), MRC Centre grant (G0601943), and the National Institutes of Neurological Diseases and Stroke and office of Rare Diseases (U54NS065712) for their support. This research was also supported by the National Institute for Health Research University College London Hospitals Biomedical Research Centre.

### **Consent for publication**

Written informed consent was obtained from the patient for the publication of this report.

### **Introduction**

Demyelinating forms of Charcot-Marie-Tooth (CMT) result from mutations in a number of genes, the majority of which show an autosomal dominant pattern of inheritance [1]. Recessive patterns of inheritance are less common. We report a case

of demyelinating CMT resulting from compound heterozygous mutation in the FGD4 gene.

### **Clinical presentation**

A 61-year-old Caucasian woman progressive unsteadiness since age 36. At age 35, she was diagnosed as having Friedreich's ataxia. She had not been followed-up since then. The patient recalled having dexterity difficulties and frequent falls since the age of 8. She had multiple foot surgeries. She had a normal birth and normal milestones.

There was no relevant family history. The patient had two sisters, who both died of cancer. The patient reported that her mother had clawed toes but walked normally in her 90's. Past medical history included arterial hypertension and a hip replacement at the age of 52. The patient was smoking and was not drinking alcohol excessively.

Examination revealed kyphoscoliosis. Neurological examination showed normal cranial nerves, apart from broken pursuit eye movements. There was no nystagmus. There was mild finger to nose ataxia and more prominent heel to shin and gait ataxia. She could walk using bilateral support. She had mild pes cavus and deformed feet. There was bilateral foot drop. Her right leg was weaker compared to the left, following the hip replacement. She had distal weakness (MRC 4) in both hands. She was areflexic.

She had severe sensory loss (pinprick and proprioception) in both arms up to the elbows and both legs up to the knees. Vibration sensation was absent in the limbs. Romberg's sign was positive.

Routine blood tests, vitamin B12, folate and immunology testing were normal or negative. She had increased thyroglobulin and thyroid peroxidase antibodies, but thyroid function testing was normal.

MRI of the brain was unremarkable.

Nerve conduction studies showed absent sensory responses. Motor conduction studies showed reduced amplitudes (0.5 – 1.2mV) and severely reduced velocities (8-14 m/sec).

Genetic screening for the chromosome 17 duplication and for mutations in PMP22, MPZ, NEFL, GDAP1, GJB1, EGR2 and the common mitochondrial mutations (MELAS, MERRF and NARP) were all negative. Next generation sequencing analysis of a panel of 14 genes (GJB1, EGR2, FGD4, FIG4, GADP1, LITAF, MPZ, MTMR2, NDRG1, NEFL, PMP22, PRX, SBF2, SH3TC2) implicated in CMT1 revealed two heterozygous likely pathogenic variants in *FGD4*: c.[1192-48\_1233del];[1304\_1305delinsAA] p.({?);(Arg435Gln)]. Neither mutation has been previously reported on public normal variant databases (dbSNP, NHLBI, exome variant server and ExAC). The c.1192-48\_1233del p.(?) mutation is a 90 bp deletion encompassing the intron 9 / exon 10 boundary and is predicted to result in a truncated and/or frameshifted transcript

and a loss of function. The c.1394\_1305delinsAA p.(Arg435Gln) missense mutation occurs at a highly conserved amino acid within the plekstrin homology domain, a domain in which a pathogenic recessive missense mutation has previously been reported (p.Arg442His PMID 22734899). As this missense mutation resides within the 90 bp deletion in the first mutation, we were able to confirm autosomal recessive inheritance by Sanger sequencing showing that these two mutations were present on separate alleles despite not having her parents DNA available.

### Discussion

CMT type 4 is the term commonly used to describe autosomal recessive CMT1 (ARCMT1) cases although some also classify the autosomal recessive CMT2 ARCM2 cases as CMT4 [2]. CMT type 4H is characterized by an early onset (up to the age of 10 years) demyelinating neuropathy, with slow progression and scoliosis [3]. The diagnosis is established by the presence of biallelic FGD4 pathogenic variants.

In the case described here there was no clear family history of neuropathy. The presence of kyphoscoliosis, however, in combination with the very severe neuropathy as indicated by the NCS pointed towards CMT4.

Sensory ataxia when severe can be difficult to distinguish from cerebellar ataxia. Nerve conduction studies in such patients are essential in deciding which gene panels to pursue based on the type and severity of the neuropathy. This case also illustrates the need for up to date review of patients labeled as having a particular genetic disease prior to the availability of genetic testing for confirmation.

## References

1. Bird TD. Charcot-Marie-Tooth Neuropathy Type 1. In: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LH, Bird TD, Fong CT, Mefford HC, Smith RJH, Stephens K, editors. SourceGeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2016. 1998 Aug 31 [updated 2015 Mar 26].
2. Rossor AM, Tomaselli PJ, Reilly MM. Recent advances in the genetic neuropathies. *Curr Opin Neurol*. 2016 Oct;29(5):537-48
3. Delague V. Charcot-Marie-Tooth Neuropathy Type 4H. In: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LH, Bird TD, Ledbetter N, Mefford HC, Smith RJH, Stephens K, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2016. 2013 Aug 8.